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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/693,908	10/23/2000	Paul L. Hermonat	023533/0130	8355

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EXAMINER
CHISM, BILLY D

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/693,908	HERMONAT, PAUL L.	
	Examiner	Art Unit	
	B. Dell Chism	1654	

-- The MAILING DATE of this communication app ars on th cov r she t with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4-20 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-18, 20 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office Action is in response to the Paper No. 14, file January 08, 2003, wherein Applicants canceled claims 3 and 47. Claims 2, 4-20 and 46 are under consideration by the Examiner.

Withdrawal of Objections and Rejections

The rejections and/or objections made in the prior office action, which are not explicitly stated below, in original or modified form are withdrawn.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. (Maintained) Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have not met the requirement of the rejection regarding the metes and bounds of the phrase "minimum number of amino acids." Thus, this rejection is maintained. Applicants state that by the inclusion of SEQ ID NO: 6 to claim 2, that claim 7 is no longer indefinite as the sequence defines the minimum number of amino acids required for the claimed DNA binding, however, this is not the case. Claim 2 does not disclose SEQ ID NO: 6 as the minimum number of amino acids required, thus, there is no antecedent basis for stating that the sequence is such. In fact, claim 7 states "a truncated" AAV REP protein, not "the truncated" AAV Rep protein. Furthermore, claim 6 states that the modified protein of claim 2 can be a wild-type AAV Rep78 protein containing amino acid substitutions, internal deletions and a combination thereof. Thus, with the claim 6 limitations on the modified

protein of claim 2, it is clear that Applicants have not met the requirement for stating the metes and bound of "minimum number of amino acids." The Examiner wishes to again state that giving the procedure to determine the minimum number of amino acids required for binding does not address the metes and bounds of the stated claim 7. Therefore, the rejection is maintained.

(New) Claims 4 and 5 are rejected as indefinite as the claims regarding the no- and weak-DNA binding. Applicants should consider the following amendments to claims 4 and 5:

4. The AAV Rep78 mutant of claim 2, wherein said AAV Rep78 modified protein [have] has no DNA binding or weak DNA binding to said DNA sequence obtained from at least one of a papillomavirus, an AAV, an oncogene or a HIV [that], and wherein the no DNA binding or weak DNA binding results in the generation of higher levels of AAV DNA replication and virion numbers compared to the corresponding wild type AAV Rep78 protein.

5. The AAV Rep78 mutant of claim 2, wherein said AAV Rep78 modified protein [having] has enhanced DNA binding to said DNA sequence obtained from at least one of a papillomavirus or an oncogene [that], and wherein the enhanced DNA binding results in enhanced inhibition of at least one of a papillomavirus or an oncoprotein compared to the corresponding wild type AAV Rep78 protein.

(New) Claims 13 and 46 are rejected for being indefinite regarding claiming that binding results in AAV DNA replication and/or AAV virion production. Claim 2 and 13 are drawn to no binding, weak binding and enhanced binding, thus, it us unclear if claims 13 and 46 apply to all three binding categories.

Claims 8-10, 12 and 14-18 are rejected for depending from rejected claims.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 20 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro administration of the AAV Rep78 mutant for replication studies, it is not enabled for in vivo therapeutic uses. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C.

112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to an in vivo method of treating any/all papillomavirus-associated disease, cancer or a HIV-associated disease comprising administration of a therapeutic composition comprising an AAV Rep78 mutant.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that the therapeutic administration of compositions for in vivo treatment of tumors and for AIDS are highly variable with their inabilities to reach target areas such as tumors or the solubility of the compounds upon in vivo administration. Jain *et al.* 1990 (Cancer and Metastasis Reviews, 9 :253-256) ; Rice *et al.* 1995 (Advances in Pharmacology, Vol. 33, pages 389-438). The claims encompass *in vivo* cancer therapy. Those of skill in the art recognize that, although *in vitro* assays are generally useful to screen the effects of agents on target cells *in vitro*, clinical correlation with treatment of cancer *in vivo* does not necessarily follow. The greatly increased complexity of *in vivo* therapy compared to the narrowly defined and controlled conditions of an *in vitro* assay does not permit a direct extrapolation of *in vitro* assay results to mammal or human therapy with any degree of predictability. *In vitro* assays cannot adequately assess cell to cell interactions which may be important in a particular pathological state. In an *in vitro* assay, the

agent is in direct contact with target cells during the entire exposure period, whereas in *in vivo* therapy, exposure at the target site may be delayed and/or reduced. See Jain et al., Cancer and Metastasis Review, 9: 253-266, for a discussion of the differences between *in vitro* assay and *in vivo* therapy and the numerous pitfalls associated with *in vivo* cancer therapy.

The amount of direction or guidance present and the presence or absence of working examples: Given the teachings of unpredictability regarding the in vivo use of pharmaceuticals for treatment of any/all papillomavirus-associated disease, cancer or HIV, there is a need for adequate working examples and direction for the making and using of the claimed invention commensurate with the what is claimed. However, the specification is lacking in adequate direction and working examples for the claimed in vivo usage.

The breadth of the claims and the quantity of experimentation needed: Given the teachings of unpredictability found in the art regarding the in vivo use of pharmaceuticals for treatment of any/all papillomavirus-associated disease, cancer or HIV, and given the lack of direction and/or working examples in the specification, there is a burden of undue experimentation for one skilled in the art to make and use claimed invention for the treatemetn of any/all papillomavirus-associated diseases, cancers or HIV-associated diseases. Thus, the specification is not enabled for the scope of the claimed invention. There is no support for in vivo administration nor is there support for treatment of any/all papillomavirus-associated disease, cancer or HIV-associated diseases.

5. (New) Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification lacks complete deposit information for the deposit of AAV Rep-77^{LG}, AAV Rep-79^{FA} and AAV Rep-192^{HG}. While the specification provides enough information for one of skill in the art to produce AAV Rep-77^{LG}, AAV Rep-79^{FA} and AAV Rep-192^{HG} with the same or similar properties as AAV Rep-77^{LG}, AAV Rep-79^{FA} and AAV Rep-192^{HG}, reproduction of an identical AAV Rep-77^{LG}, AAV Rep-79^{FA} and AAV Rep-192^{HG} are an unpredictable event. Because it does not appear that AAV Rep-77^{LG}, AAV Rep-79^{FA} and AAV Rep-192^{HG} are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because certain of the claims specially require the use of AAV Rep-77^{LG}, AAV Rep-79^{FA} and AAV Rep-192^{HG}, a suitable deposit of AAV Rep-77^{LG}, AAV Rep-79^{FA} and AAV Rep-192^{HG} for patent purposes is required or evidence must be provided that AAV Rep-77^{LG}, AAV Rep-79^{FA} and AAV Rep-192^{HG} are well known and readily available to the public.

Furthermore, unless the deposit was made at or before the time of filing, a declaration fuled under the 37 C.F.R. 1/132 is necessary to construct a chain of custody. The declaration, executed by a person in a position to know, should identify the deposited AAV Rep-77^{LG},AAV Rep-79^{FA} and AAV Rep-192^{HG} by its depository accession number, establish that the deposited AAV Rep-77^{LG},AAV Rep-79^{FA} and AAV Rep-192^{HG} are the same as that described in the specification, and establish that the deposited AAV Rep-77^{LG},AAV Rep-79^{FA} and AAV Rep-192^{HG} were in applicants' possession at the time of filing. See In re Lundak, 773 F.2d. 1216, 227 U.S.P.Q. 90 (Fed. Cir. 1985).

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, name and address of the depository, and the complete taxonomic description.

As a possible means of completing the record, Applicants' may submit a copy of the deposit receipt.

Conclusion

Due to new grounds of rejection, this action is made NON-FINAL.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to B. Dell Chism whose telephone number is 703-306-5815. The examiner can normally be reached on 7:30 AM - 4:30 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 703-306-3220. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

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B. Dell Chism
March 10, 2003

BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600